

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) A computer implemented method for modeling ligand-protein binding interactions, comprising:

providing structural information describing the structure of a protein and each ligand in a set of one or more ligands;

using the structural information for the protein to identify a binding region of the protein;

identifying a plurality of preferred binding conformations for each ligand in ~~of the set of~~ ligands in the binding region, the preferred binding conformations being determined by generating and ranking initial conformations for each ligand in the set of ligands at the binding region using docking techniques;

optimizing the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

calculating a binding energy for each ligand in ~~of the set of~~ ligands in the corresponding optimized preferred binding conformations; and

selecting for each ligand in ~~each of the set of~~ ligands the lowest calculated binding energy in the optimized preferred binding conformations, and outputting the selected calculated binding energies as the predicted binding energies for the predicted binding conformations ~~for each of the~~ set of ligands.

2. (Original) The method of claim 1, wherein:

the binding region is a known binding region defined by the structural information.

3. (Currently Amended) The method of claim 1, wherein:

the binding region is an unknown binding region; and
using the structural information for the protein to identify a binding region of the ligand
~~in the protein~~ comprises predicting a probable binding region based at least in part on the
structural information.

4. (Currently Amended) The method of claim 3, wherein using the structural
information to identify a binding region of the protein ~~predicting a probable binding region~~
comprises:

mapping the empty volumes available for ligand binding in the protein to identify one or
more potential binding regions;

generating initial conformations for one or more ligands known to bind the protein using
docking techniques in each of the one or more potential binding regions and scoring a
preliminary energy function for at least some of the initial conformations;

selecting from the initial conformations for each of the known ligands a plurality of best
conformations in each of the potential binding regions based at least in part on the preliminary
energy scores;

~~and scoring an energy function for each of the best conformations; and~~

identifying the probable binding site based on a spatial location of the best conformations
~~having the lowest energy scores.~~

5. (Currently Amended) The method of claim 4, further comprising:

~~before scoring the energy function for each of the best conformations,~~ optimizing the
selected best conformations to obtain a set of energy-minimized conformations for each of the
known ligands in each of the potential binding regions and scoring a second preliminary energy
function for each of the best conformations;

wherein identifying the probable binding site is based on a spatial location of the best
conformations having the lowest second preliminary energy scores. ~~wherein the energy function
is scored for each of the energy-minimized conformations.~~

6. (Currently Amended) The method of claim 4, further comprising:
before scoring the preliminary energy function for each of the best conformations,
calculating for each of the best conformations a percentage of the ligand surface area buried
within the protein for the conformation;
wherein the preliminary energy function is scored only for a subset of the best
conformations, wherein each of the best conformations in the subset has having a calculated
percentage of the ligand surface area buried within the protein which exceedsing a predetermined
surface area threshold.
7. (Cancelled)
8. (Currently Amended) The method of claim 7~~1~~, ~~further comprising~~wherein:
identifying a plurality of preferred binding conformations includes ~~after selecting the best~~
~~conformations~~, optimizing the selected best conformations to obtain a set of energy-minimized
conformations for each of the ligands;
wherein the preferred binding conformations comprise the energy-minimized
conformations.
9. (Original) The method of claim 1, wherein:
the annealing molecular dynamics includes a full atom force field.
10. (Original) The method of claim 1, wherein:
the solvation effects include a continuum description of solvation.
11. (Original) The method of claim 1, wherein:
the solvation effects include a surface-area based solvation model.

12. (Currently Amended) The method of claim 1, wherein:
calculating a binding energy for each ligand in of the set of ligands includes taking the difference in the ligand energy in the receptorprotein and in solution.

13. (Original) The method of claim 1, wherein:
the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the ligand in water from the energy of the ligand in the protein.

14. (Original) The method of claim 1, wherein:
the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein.

15. (Original) The method of claim 1, further comprising:
identifying from the set of ligands one or more ligands predicted to have high binding affinity based on the calculated binding energy of the ligands in the binding site.

16. (Original) The method of claim 1, wherein:
the protein is a globular protein or a transmembrane protein.

17-28. (Withdrawn)

29. (Currently Amended) A computational model of a ligand-protein complex for a protein having an unknown binding site, the model comprising:
a computer-readable memory storing data describing an optimized preferred binding conformation for the protein and a ligand known to bind to the protein, the optimized binding conformation being generated according to the method of claim 1.

30. (Withdrawn)

31. (Currently Amended) A computer program product on a computer-readable medium for modeling ligand-protein binding interactions, the computer program product comprising instructions operable to cause a programmable processor to:

provide structural information describing the structure of a protein and each ligand in a set of one or more ligands;

use the structural information for the protein to identify a binding region of the protein;

identify a plurality of preferred binding conformations for each ligand in ~~of the~~ set of ligands in the binding region, the preferred binding conformations being determined by generating and ranking initial conformations for each ligand in the set of ligands at the binding region using docking techniques;

optimize the preferred binding conformations using annealing molecular dynamics, the annealing molecular dynamics including solvation effects;

calculate a binding energy for each ligand in ~~of the~~ set of ligands in the corresponding optimized preferred binding conformations; ~~and~~

select for each ligand in ~~of the~~ set of ligands the lowest calculated binding energy in the optimized preferred binding conformations, and output the selected calculated binding energies as the predicted binding energies for the predicted binding conformations for each of the set of ligands.

32-35. (Withdrawn)

36. (New) The computer program product of claim 31, wherein instructions to use the structural information to identify a binding region of the protein comprises instructions to:

map the empty volumes available for ligand binding in the protein to identify one or more potential binding regions;

generate initial conformations for one or more ligands known to bind the protein using docking techniques in each of the one or more potential binding regions and scoring a preliminary energy function for at least some of the initial conformations;

select from the initial conformations for each of the known ligands a plurality of best conformations in each of the potential binding regions based at least in part on the preliminary energy scores; and

identify the probable binding site based on a spatial location of the best conformations.

37. (New) The computer program product of claim 31, wherein:
the annealing molecular dynamics includes a full atom force field.

38. (New) The computer program product of claim 31, wherein:
the solvation effects include a continuum description of solvation.

39. (New) The computer program product of claim 31, wherein:
the solvation effects include a surface-area based solvation model.

40. (New) The computer program product of claim 31, wherein:
instructions to calculate a binding energy for ligand in the set of ligands includes taking the difference in the ligand energy in the protein and in solution.

41. (New) The computer program product of claim 31, wherein:
the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the ligand in water from the energy of the ligand in the protein.

42. (New) The computer program product of claim 31, wherein:

the binding energy is calculated for a ligand according to a scoring function comprising subtracting the free energy of the protein and the free energy of the ligand from the free energy of the ligand in the protein.

43. (New) The computer program product of claim 31, further comprising instructions to:

identify from the set of ligands one or more ligands predicted to have high binding affinity based on the calculated binding energy of the ligands in the binding site.

44. (New) The computer program product of claim 31, wherein:
generating and ranking initial conformations includes scoring an energy function for at least some of the initial conformations and ranking the initial conformations based at least in part on the energy scores.

45. (New) The computer program product of claim 31, wherein:
generating and ranking initial conformations includes determining a percentage of the ligand surface area buried within the protein for each of the initial conformations and determining energy scores only for a subset of the preferred conformations, wherein each of the preferred conformations in the subset has a calculated percentage of the ligand surface area buried within the protein which exceeds a predetermined threshold.